Trial Designs

PREVENTION

# Rationale and Design of LAPLACE-2: A Phase 3, Randomized, Double-Blind, Placebo- and Ezetimibe-Controlled Trial Evaluating the Efficacy and Safety of Evolocumab in Subjects With Hypercholesterolemia on Background Statin Therapy

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ABSTRACT

Low-density lipoprotein cholesterol (LDL-C) levels are significantly associated with atherosclerotic cardiovascular disease (ASCVD) risk, and studies using interventions that lower LDL-C levels have been shown to reduce the risk of ASCVD events and mortality. Statin treatment is the current first-line therapy for lowering LDL-C and reducing ASCVD risk. However, many patients are still unable to reach recommended LDL-C goals on maximally tolerated statin therapy. Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9, including evolocumab (previously AMG 145), dramatically lowered LDL-C in phase 2 clinical trials when administered alone or in combination with a statin. The aim of this phase 3 study is to evaluate the efficacy of 12 weeks of subcutaneous evolocumab (vs placebo) administered every 2 weeks or every month in combination with a statin in patients with hypercholesterolemia and mixed dyslipidemia. This study will also provide comparative efficacy, safety, and tolerability data between evolocumab and ezetimibe when added to background atorvastatin therapy.

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## Introduction

Abnormal lipid levels, including elevated low-density lipoprotein cholesterol (LDL-C), are associated with an increased risk for atherosclerotic cardiovascular disease (ASCVD) events[1] and mortality.[2] As a consequence, LDL-C reduction has been the focus of recent prevention recommendations.[3,4] Based on extensive data from randomized trials, statins are the current first-line therapy for dyslipidemia, and their use is linked to reductions in ASCVD events and both ASCVD mortality and total-cause mortality in proportion to the degree of LDL-C lowering.[5]

Nonetheless, there are unmet clinical needs and evidence gaps in the statin era. Several cholesterol treatment guidelines have recommended achievement of LDL-C levels <100 mg/dL (2.6 mmol/L) or <70 mg/dL (1.8 mmol/L) depending on the level of risk.[3,4,6,7] However, many high-risk patients fail to reach the LDL-C goal of <100 mg/dL (2.6 mmol/L),[8] and few individuals on high-intensity statin therapy achieve LDL-C levels <70 mg/dL (1.8 mmol/L).[9,10] These recommendations and the desire to provide clinicians with data to support treatment decisions formed the basis for the design of the LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy 2 (LAPLACE-2) trial. More recently, the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines have moved away from LDL-C treatment targets after a systematic review of data from randomized cardiovascular outcomes trials.[11] However, they recommended as indicators of adequacy of therapy a >50% reduction in LDL-C for individuals with clinical ASCVD or baseline LDL-C ≥190 mg/dL, and LDL-C reductions of at least 30% to 50% for those with diabetes and for primary prevention in individuals at increased ASCVD risk. Data are not yet available to determine how often patients are treated as recommended by the 2013 ACC/AHA cholesterol guidelines, but most will need treatment with at least a high-intensity statin to achieve a 50% reduction in LDL-C.[9,10] Intolerance to statin therapy is common and results in suboptimal ASCVD prevention.[12,13] In addition, an important scientific question remains regarding the optimal LDL-C treatment targets for ASCVD prevention. Many statin-treated individuals experience ASCVD events,[14] suggesting that further LDL-C lowering may result in additional risk reduction.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease involved in low-density lipoprotein receptor (LDLR) regulation. By binding to LDLRs on the surface of hepatocytes, the presence of PCSK9 leads to receptor degradation.[15] Humans with PCSK9 loss-of-function mutations have low levels of LDL-C and a lower risk of coronary heart disease, but are otherwise healthy,[16,17] whereas humans with PCSK9 gain-of-function mutations have elevated LDL-C levels and are at increased risk for ASCVD.[18,19] Thus, PCSK9 is a promising target for LDL-C reduction.

Evolocumab is a fully human monoclonal antibody against PCSK9. By binding to circulating PCSK9, evolocumab prevents PCSK9 from binding to LDLRs, indirectly enhancing LDLR recycling to the hepatocyte surface.[20] The prevention of LDLR degradation thus increases the clearance of cholesterol-containing LDL particles, resulting in a dramatic decrease in serum LDL-C levels and improvements in other serum lipid levels.[21] Recently, the efficacy and safety of evolocumab has been examined in >1200 subjects from 4 phase 2 studies.[22–26] Treatment with evolocumab significantly lowers LDL-C by up to 50% to 70% in patients with elevated LDL-C, including those who are statin intolerant,[26] have heterozygous familial hypercholesterolemia,[25] are on no current lipid-modifying therapy,[24] or are currently being treated with a statin.[23]

Response to subcutaneous (SC) evolocumab in subjects receiving concomitant oral statin therapy was explored in LAPLACE–Thrombolysis In Myocardial Infarction (TIMI) 57 (LAPLACE-1), a 12-week, phase 2, double-blind, placebo-controlled, multicenter study.[22,23] This was the largest phase 2 PCSK9-inhibitor study to date—631 subjects were randomized to 1 of 8 treatment arms to evaluate the efficacy, tolerability, and safety of various doses of evolocumab vs placebo in subjects with hypercholesterolemia already taking a stable dose of statin. Because statins raise PCSK9 levels,[27] LAPLACE-TIMI 57 provided an opportunity to assess the effects of different doses and dose frequencies of evolocumab in subjects on stable background statin therapy compared with placebo. Concomitant treatment with evolocumab and a statin was associated with a reduction of up to 66% in LDL-C levels (placebo adjusted).[23] However, LAPLACE-TIMI 57 was not designed to compare the effect of evolocumab among patients taking specific background statins and statin doses.

LAPLACE-2 is a phase 3 trial designed to assess LDL-C response to evolocumab compared with placebo in subjects randomized to 1 of 3 commonly prescribed statins while providing comparative data against ezetimibe.

## Methods

### Study Design and Objectives

LAPLACE-2 (NCT01763866) is a 12-week, randomized, double-blind, placebo- and ezetimibe-controlled, phase 3, multicenter study to examine the efficacy and safety of evolocumab in combination with stable statin therapy in subjects with primary hypercholesterolemia and mixed dyslipidemia. The primary objective of this study is to evaluate the efficacy (vs placebo) of 12 weeks of SC evolocumab administered every 2 weeks (Q2W) or every month (QM) when used in combination with a statin on percentage change from baseline in LDL-C. The secondary objectives of this study are 3-fold: (1) evaluate the safety and tolerability (vs placebo or ezetimibe) of SC evolocumab Q2W or QM in combination with a statin; (2) assess the effects of 12 weeks of evolocumab used in combination with a statin on change from baseline in LDL-C and percentage change from baseline in a number of additional lipid parameters (eg, high-density lipoprotein cholesterol [HDL-C], non–HDL-C, triglycerides, lipoprotein a [Lp(a)], and very low-density lipoprotein cholesterol [VLDL-C]) compared with placebo or ezetimibe; and (3) assess the effects of 12 weeks of evolocumab treatment compared with ezetimibe on the number of subjects reaching the LDL-C goal of <70 mg/dL (1.8 mmol/L).


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## Study Hypothesis

The primary hypothesis is that both dosing regimens of evolocumab, SC 140 mg Q2W and 420 mg QM, will be well tolerated and will result in greater reduction of LDL-C than placebo or ezetimibe when used in combination with a statin in subjects with primary hypercholesterolemia and mixed dyslipidemia.

Table 1. Eligibility Criteria

| |
|---|
| Exclusion Criteria |
| Age 18 to 80 years, inclusive |
| Intensive[a] statin dose + fasting LDL-C ≥80 mg/dL (2.1 mmol/L) |
| OR nonintensive[a] statin dose + fasting LDL-C ≥100 mg/dL (2.6 mmol/L) |
| OR no statin + fasting LDL-C ≥150 mg/dL (4.0 mmol/L) |
| Fasting triglycerides ≤400 mg/dL (4.5 mmol/L) |
| Exclusion Criteria |
| Cardiovascular |
| NYHA class III or IV, or last known LVEF <30% |
| Uncontrolled serious cardiac arrhythmia ≤3 months prior to randomization |
| MI/UA, PCI, CABG, or stroke ≤6 mo prior to randomization |
| Planned cardiac surgery or revascularization |
| Type 1 DM; newly diagnosed or poorly controlled type 2 DM ($HbA_{1c}$ >8.5%) |
| SBP >160 mm Hg or DBP >100 mm Hg |
| Medications |
| ≤6 wk prior to screening: bile acid–sequestering resins, fibrates or derivatives, red yeast rice, >200 mg/day niacin, or >1000 mg/day omega-3 fatty acids |
| ≤3 mo prior to screening: cyclosporine, systemic steroids, vitamin A derivatives,[b] or retinol derivatives |
| ≤12 mo prior to screening: CETP inhibitors |
| Laboratory |
| TSH < LLN or TSH >1.5× ULN |
| eGFR <30 mL/min/1.73m² |
| AST or ALT >2× ULN |
| CK >3× ULN |
| Known illnesses |
| Active infection |
| Major hematologic, renal, metabolic, GI, or endocrine disruption |
| DVT or pulmonary embolism (within 3 mo) |
| Other |
| Current/prior history of statin intolerance |
| Requires, per investigator's opinion, maximal statin dosage |
| Personal or family history of hereditary muscular disorders |
| Pregnant or currently breastfeeding |
| Previously received evolocumab or any other investigational therapy to inhibit PCSK9 |

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CABG, coronary artery bypass graft; CETP, cholesterylester transfer protein; CK, creatine kinase; DBP, diastolic blood pressure; DM, diabetes mellitus; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; $HbA_{1c}$, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; QD, daily; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone; UA, unstable angina; ULN, upper limit of normal.
[a]Intensive statin use was defined as the following: simvastatin 80 mg QD, atorvastatin ≥40 mg QD, rosuvastatin ≥20 mg QD, or any statin + ezetimibe. Nonintensive statin use was defined as 1 record of previous statin usage that did not qualify as intensive statin use.
[b]Vitamin A in a multivitamin was permitted.

## Study Population

Eligibility criteria are summarized in Table 1. Briefly, subjects 18 to 80 years of age were eligible for the study if they had a central laboratory fasting LDL-C at screening of ≥150 mg/dL (4.0 mmol/L; no statin at screening), ≥100 mg/dL (2.6 mmol/L; nonintensive statin at screening), or ≥80 mg/dL (2.1 mmol/L; intensive statin at screening). Intensive statin use was defined as simvastatin 80 mg daily (QD), atorvastatin ≥40 mg QD, rosuvastatin ≥20 mg QD, or any statin plus ezetimibe. Fasting triglycerides were required to be ≤400 mg/dL (4.5 mmol/L) by central laboratory at screening. Exclusion criteria focused on safety and conditions that could influence efficacy (Table 1). Clinical investigations were in accordance with the Declaration of Helsinki.

## Screening and Enrollment Procedures

The screening and enrollment procedures are outlined in the Figure 1. During screening, written informed consent was collected and a physical examination conducted (including vital signs and height, patient medical history, concomitant therapy, 12-lead electrocardiogram [triplicate], adverse events [AEs], and serious adverse events [SAEs]). Blood was drawn to assess fasting (≥9 hours) lipids, chemistry, hematology, pregnancy status (women of childbearing age), and follicle-stimulating hormone (if required to ensure menopause in female subjects). Because the LDLR is thought to be involved in hepatitis C virus (HCV) entry into the hepatocyte,[28–30] there exists the theoretical possibility that LDLR upregulation via PCSK9 inhibition could increase the risk of infection with HCV. Subjects at high risk for or with a history of HCV infection, or those with aspartate aminotransferase or alanine aminotransferase >2× upper limit of normal during screening, underwent testing for HCV. Subjects who tested positive were monitored monthly for viral load.

Following screening, eligible subjects entered into a placebo run-in period to assess tolerance for SC


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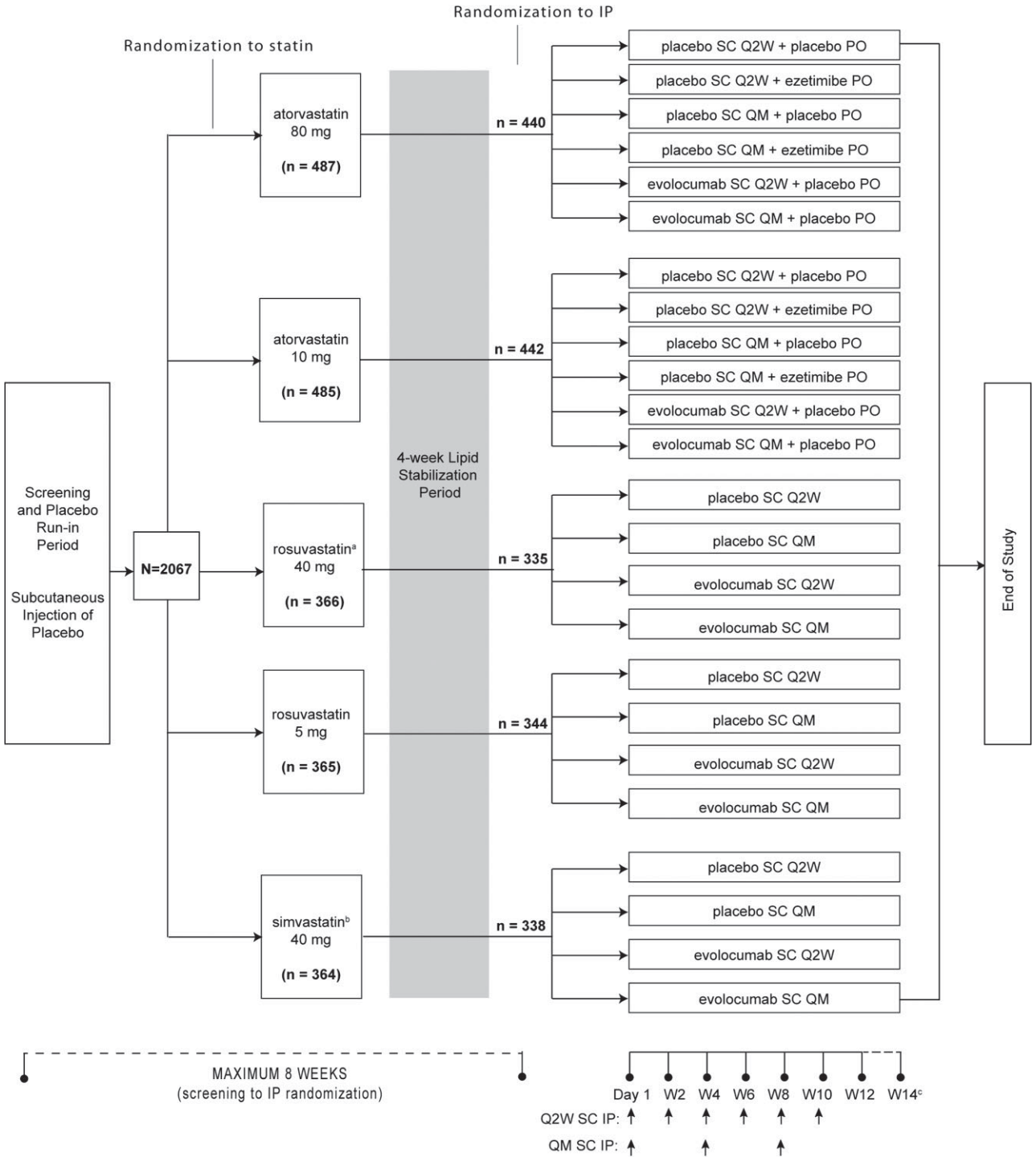


Figure 1. Treatment schema. Subjects who fulfilled the inclusion/exclusion criteria and completed the placebo run-in period were assigned to 1 of 5 statin treatment arms. Following 4 weeks of stable lipid therapy, subjects were randomized to evolocumab, placebo, or ezetimibe (atorvastatin treatment arms only). Evolocumab Q2W dosage was 140 mg; evolocumab QM dose was 420 mg. Administration of study drug is indicated with a vertical arrow. Results are based on a data cut taken September 23, 2013. Abbreviations: CrCl, creatinine clearance; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; PO, oral; Q2W, every 2 weeks; QM, every month; SAE, serious adverse event; SC, subcutaneous; W, week. [a] Subjects with moderate renal impairment (CrCl <60 mL/min) and Asian subjects who were randomized to the rosuvastatin maximum-dose arm received rosuvastatin 20 mg. [b] Subjects randomized to simvastatin and on contraindicated therapies were assigned a lower dose (either 10 or 20 mg). [c] Phone call for SAEs for subjects receiving SC IP administration Q2W.


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administration of placebo. Subjects who completed screening and tolerated the placebo injection were then randomized to 1 of 5 daily, open-label, background statin treatments: rosuvastatin 5 mg QD, rosuvastatin 40 mg QD, atorvastatin 10 mg QD, atorvastatin 80 mg QD, or simvastatin 40 mg QD (Figure 1); statin assignment and dose were random and not associated with prerandomization statin therapy dose or intensity. Given current regional restrictions on simvastatin dosing, only the 40-mg simvastatin dose was used in the study.[31] Global labeling precautions for the statins were followed: Asian subjects or those with moderate renal impairment (creatinine clearance <60 mL/min) who were randomized to maximal dose rosuvastatin instead received 20 mg of rosuvastatin QD; subjects using certain concomitant medications were assigned a lower dose of simvastatin (10 or 20 mg QD) to reduce the risk of muscle-related side effects; and colchicine use was prohibited due to the risk of myopathy when combined with atorvastatin or simvastatin. Subjects were also prohibited from taking concomitant medications that could influence safety or efficacy assessments (Table 2).

Table 2. Prohibited Medications

| |
|---|
| **Prohibited lipid-lowering medications** |
| Fibrate derivatives |
| Bile acid–sequestering resins |
| Statins (outside of what was provided as background therapy during the study) |
| Ezetimibe (outside of what was provided as background therapy during the study) |
| Red yeast rice |
| Niacin (>200 mg/d) |
| Omega-3 fatty acids (eg, EPA and DHA) >1000 mg/d |
| **Prohibited drugs that significantly affect lipid metabolism** |
| Systemic cyclosporine |
| Systemic steroids |
| Vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions[a] |
| Amphetamines or amphetamine derivatives |
| Weight-loss medications |
| **Prohibited medications or foods that potently inhibit CYP3A** |
| Itraconazole, ketoconazole, or other antifungal azoles |
| Erythromycin and clarithromycin (macrolide antibiotics) |
| Telithromycin (ketolide antibiotic) |
| HIV or HCV protease inhibitors |
| Nefazodone (antidepressant) |
| >1 quart daily of grapefruit juice |

Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus.
[a]Vitamin A as part of a multivitamin preparation was permitted.

## Lipid-Stabilization Period and Randomization to Investigational Product

To obtain stable baseline lipid values and ensure subjects were able to tolerate statins, all subjects (irrespective of prior statin usage) entered a 4-week lipid-stabilization period on their assigned statin. Subjects who successfully completed this period were then randomized to evolocumab, placebo, and/or ezetimibe, as shown in the Figure 1. Subjects taking rosuvastatin or simvastatin were then randomized (double blinded) to either evolocumab 140 mg or placebo SC Q2W, or evolocumab 420 mg or placebo SC QM. Within each dose-frequency group, patients were administered matching volumes of either placebo or evolocumab to maintain blinding. Subjects randomized to the atorvastatin treatment arm underwent an additional randomization (double blind, double dummy) to evolocumab 140 mg SC Q2W and oral (PO) placebo, evolocumab 420 mg SC QM and placebo PO, or ezetimibe 10 mg/day PO and placebo SC Q2W or QM.

## Treatment Protocol

After the lipid-stabilization phase completed, subjects were randomized to investigational product (IP) on the day-1 study visit and returned to the study site at weeks 2, 8, 10, and 12. The IP (ie, evolocumab or SC placebo) was provided in a spring-based prefilled autoinjector/pen device. The IP was administered in the clinic on day 1 and weeks 2, 8, and 10 for Q2W subjects, and on day 1 and week 8 for QM subjects. In a nonclinic setting (eg, home), IP was self-administered on weeks 4 and 6 by Q2W subjects and on week 4 by QM subjects. At all study site visits, a physical examination including vital signs (blood pressure and heart rate) was performed, AE/SAEs were collected, and cardiovascular (CV) events were recorded. The final study visit occurred 30 days after last dose of IP; Q2W subjects were contacted at week 14 via phone to collect AEs/SAEs and CV events.

Subjects were counseled to maintain a stable diet and comply with all allowed lipid-lowering medication that they were prescribed. Investigators were instructed to encourage participants who discontinued IP early to continue with the data collection, including endpoints and AEs. If a subject withdrew from the study early, investigators were instructed to complete and report observations as thoroughly as possible up to the date of withdrawal, and to complete week-12 procedures at the time of withdrawal (including endpoints, AE/SAEs, and CV events).

Central laboratory results of the lipid panel—including LDL-C, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and Lp(a)—and high-sensitivity C-reactive protein were blinded throughout the study. LDL-C was calculated by the Friedewald formula, with reflexive testing via ultracentrifugation (UC) when calculated LDL-C was <40 mg/dL (1.0 mmol/L) or triglyceride levels were >400 mg/dL (3.9 mmol/L). For methodologies for other lipid parameters, see Supplemental Materials.

## Study Endpoints

The co-primary endpoints were (1) the mean percentage change from baseline in LDL-C at week 10 and 12 and (2)


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the percentage change from baseline in LDL-C at week 12. There were multiple secondary efficacy endpoints for this study: change from baseline in LDL-C; percentage change from baseline in non–HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, Lp(a), triglycerides, HDL-C, and VLDL-C; and LDL-C response rate (proportion of subjects achieving LDL-C <70 mg/dL [1.8 mmol/L]). Secondary endpoints were calculated for both the average of week 10 and 12 scores and for week 12 alone.

Safety endpoints included subject incidence of treatment-emergent AEs, laboratory values and vital signs at each scheduled visit, electrocardiographic parameters at each scheduled visit, and the incidence of anti-evolocumab antibodies (binding and neutralizing). Exploratory safety endpoints included adjudicated CV events: CV death, MI, hospitalization for unstable angina, coronary revascularization, stroke, and hospitalization for heart failure.

## Statistical Design and Analysis

The expected number of subjects randomized to IP for this study was 1700, which will provide ≥98% power for testing the superiority of each evolocumab dosing regimen over placebo on the co-primary endpoints within each background statin therapy group and SC dose-frequency group. The sample size will also provide ≥92% power for testing the superiority of each evolocumab dosing regimen over ezetimibe on the co-primary endpoints within each background atorvastatin therapy and SC dose-frequency group.

Efficacy and safety analyses will include all subjects who were randomized to and received ≥1 dose of IP. Testing the primary endpoints (evolocumab vs placebo) will be conducted using a repeated-measures linear effects model; this model includes terms for treatment group, stratification factors, scheduled visit, and the interaction between treatment and scheduled visit. Missing values will not be imputed because the repeated-measures model accounts for missing data. Co-primary endpoints will be evaluated within the statin-dose groups and SC IP dose-frequency groups separately. A planned analysis will also pool results across statins within each SC IP dose-frequency group. The analysis of secondary endpoints will be similar to that of the co-primary endpoints. The proportion of subjects attaining LDL-C <100 mg/dL (2.6 mmol/L) and <130 mg/dL (3.4 mmol/L) will also be summarized for subjects assigned atorvastatin background therapy. To preserve the familywise type I error rate (0.05), a significance level of 0.05 will be allocated for comparisons of evolocumab to placebo for each of the rosuvastatin 5 mg and 40 mg and simvastatin dose cohorts; significance levels of 0.01 and 0.04 will be used for comparisons of evolocumab to placebo and ezetimibe for the atorvastatin dose cohorts, respectively. Multiplicity adjustments within each dose-frequency group and against each control arm will be made to correct for multiple endpoints. Significance testing will be 2-sided.

For the safety analysis, subject incidences of AEs for each treatment group will be summarized by both preferred term and system organ class. AEs are defined as untoward medical occurrences reported in a clinical-trial patient, including worsening of a preexisting medical condition. The safety summary will include all AEs occurring after the first dose of IP. A separate safety summary of AEs occurring only during the lipid-stabilization period will also be provided.

## Study Organization

Patients were recruited from study sites in Australia, Belgium, Canada, the Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Italy, the Netherlands, Russia, Spain, Sweden, Switzerland, the United Kingdom, and the United States.

An external, independent data-monitoring committee was established to review accumulating data from this and other completed and ongoing evolocumab phase 2 and 3 studies to ensure there is no avoidable risk or harm to subjects. Analyses for the data-monitoring committee were provided by an independent biostatistical group external to Amgen. An independent clinical events committee blinded to subject treatment group assignment adjudicated all deaths and suspected CV events reported during the study. Events adjudicated included death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure.

All laboratory assessments were conducted at the study core laboratories: Medpace Reference Laboratories (Cincinnati, OH) and Quintiles (Durham, NC). Independent, unblinded assessment of lipids or high-sensitivity C-reactive protein was prohibited.

## Results

Enrollment began on January 15, 2013; the last patient was randomized to IP on August 15, 2013. A total of 3593 subjects were screened. Of these, 2067 met the screening criteria and were enrolled and randomized to statin treatment (Figure 1); 1899 patients were subsequently randomized to IP. Baseline characteristics (data cut from September 23, 2013) are reported in Table 3. In brief, 46% of subjects were female, the mean (SD) age was 60 (10) years, and a number of patients had a history of cardiac risk factors, including hypertension (57%), metabolic syndrome (33%), or coronary artery disease (22%).

## Discussion

Based on an extensive body of data from randomized trials, statins are the mainstay of ASCVD risk-reduction therapy.[32–36] Two important areas of unmet need in the statin era are (1) how best to treat statin-intolerant individuals to optimally reduce ASCVD risk and (2) how best to achieve LDL-C goals or acceptable levels. The LAPLACE-2 trial will address the second of these unmet clinical needs. Several cholesterol treatment guidelines have recommended LDL-C goals <100 mg/dL (2.6 mmol/L) or <70 mg/dL (1.8 mmol/L).[3,4,6] In the Vytorin Versus Atorvastatin (VYVA) trial, although most participants receiving atorvastatin 80 mg achieved LDL-C levels <100 mg/dL (2.6 mmol/L), only 36% achieved LDL-C levels <70 mg/dL (1.8 mmol/L).[37] An LDL-C <70 mg/dL (1.8 mmol/L) was achieved by 64% of subjects receiving simvastatin 80 mg/day with ezetimibe 10 mg/day. Based


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on phase 2 clinical-trial data,[20] the addition of evolocumab to background statin treatment is expected to improve such goal attainment. LAPLACE-2 will provide clinicians with an estimate of the expected degree of LDL-C reduction when evolocumab is added to various doses of background statin therapy and allow comparison to the additional LDL-C reductions obtained with ezetimibe.

LAPLACE-2 was designed as a 12-week study because previous phase 2 studies in evolocumab, where its efficacy when combined with statins was examined, showed that 12 weeks is sufficient time to measure primary and secondary endpoints at peak pharmacodynamic effect.[23,25,38]

Table 3. Baseline Characteristics (N = 2067)

| Characteristic | Value |
|---|---|
| *Lipid-stabilization period summary* | |
| Subjects randomized to a statin | 2067 |
| Prerandomization screening lipids, median (Q1–Q3), mg/dL[a] | |
| LDL-C | 139 (111–175) |
| HDL-C | 51 (42–62) |
| Triglycerides | 130 (96–177) |
| Prerandomization therapy, n (%)[b] | |
| Intensive statin use | 591 (28.6) |
| Nonintensive statin use | 858 (41.5) |
| No statin use | 618 (29.9) |
| *Double-blind randomization period summary* | |
| Subjects randomized to IP | 1899 |
| Subjects with study day 1 by data cut[c] | 1896 |
| Demographics | |
| Age, y, mean (SD) | 59.8 (9.9) |
| Female sex, n (%) | 868 (45.8) |
| Race, n (%) | |
| White | 1783 (94.0) |
| Black or African American | 73 (3.9) |
| Asian | 25 (1.3) |
| Other | 15 (0.8) |
| Cardiac risk factors | |
| Clinical atherosclerotic disease, n (%) | |
| CAD | 417 (22.0) |
| PVD or CVD | 192 (10.1) |
| Type 2 DM, n (%) | 293 (15.5) |
| Hypertension, n (%) | 1072 (56.5) |
| Current cigarette use, n (%) | 290 (15.3) |
| Baseline metabolic syndrome, n (%)[d] | 623 (32.9) |
| BMI, kg/m$^2$, mean (SD)[e] | 29.5 (5.7) |

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CVD, cerebrovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; IP, investigational product; LDL-C, low-density lipoprotein cholesterol; PVD, peripheral vascular disease; QD, daily; SBP, systolic blood pressure; SD, standard deviation.
Results are based on a data cut taken on September 23, 2013.
[a]Screening lipid data only available on 1516 subjects for the data cut. [b]Intensive statin use is defined as any of simvastatin 80 mg QD, atorvastatin ≥40 mg QD, rosuvastatin ≥20 mg QD, or any statin + ezetimibe; nonintensive statin use is defined as any statin use other than those considered intensive. [c]Percentages reported are out of this subject count. Completed missing data or changes to the database after the data cut can alter count and percent tabulations. [d]Criteria for baseline metabolic syndrome are no diagnosis of type 2 DM and the presence of ≥3 of the following: elevated waist circumference (≥102 cm for non-Asian men, ≥88 cm for non-Asian women, ≥90 cm for Asian men, >80 cm for Asian women); triglycerides ≥150 mg/dL; HDL-C <40 mg/dL for men (<50 mg/dL for women); SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg, or history of hypertension; or fasting glucose ≥100 mg/dL. [e]1890 subjects had height and weight data available for the data cut.

In addition, most pivotal LDL-C–lowering studies have been 8 to 16 weeks in duration; hence, there is regulatory precedent for trial durations of this length. We chose the highest and lowest doses of atorvastatin and rosuvastatin in this study to give clinicians an idea of expected response and safety from the addition of evolocumab across dose ranges of commonly prescribed statins. Importantly, LAPLACE-2 will examine the efficacy of evolocumab in patients representative of those expected to receive PCSK9-inhibitor therapy; for example, many have preexisting cardiac risk factors and thus may benefit from additional LDL-C lowering (Table 3). Lastly, the LAPLACE-2 study will provide comparative data for evolocumab vs ezetimibe treatment in subjects taking background atorvastatin therapy. Ezetimibe is commonly added to statins to boost LDL-C lowering, but little is known about the comparative efficacy of ezetimibe vs a PCSK9 inhibitor in patients on background statin therapy. In addition, the ability to achieve LDL-C levels <100 mg/dL (2.6 mmol/L) and <70 mg/dL (1.8 mmol/L) will be compared across the various statins and statin-evolocumab and statin-ezetimibe combinations.

Statins reduce the relative risk of ASCVD events in direct proportion to the magnitude of LDL-C lowering.[36] In a meta-analysis by the Cholesterol Treatment Trialists, the relative risk of major CVD events (including coronary revascularization) was reduced by 22% for each 1-mmol/L (39 mg/dL) reduction in LDL-C.[5] Treatment with the high-intensity statin atorvastatin 80 mg in the Treating to New Targets (TNT), Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL), and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials was shown to reduce the relative risk of major CVD events by an additional 11% to 23% when compared with moderate-intensity statin therapy


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(atorvastatin 10 mg, simvastatin 20 to 40 mg, or pravastatin 40 mg).[5,9,10,39] Nonetheless, substantial proportions of the atorvastatin 80 mg-treated groups went on to experience a major CVD event during the trials (ranging from 4% to 11% per year). Mean LDL-C levels in the atorvastatin 80-mg groups ranged from 62 to 80 mg/dL (1.6–2.1 mmol/L).[9,10,39] These data suggest that further reductions in LDL-C may be warranted. Therefore, to evaluate the added ASCVD-reduction benefit of very aggressive LDL-C lowering, evolocumab is being compared with placebo in a CV outcomes trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk [FOURIER]) performed in very high-risk individuals treated with high-intensity statin therapy with a baseline LDL-C >70 mg/dL (1.8 mmol/L).[36] Because many evolocumab-treated participants will be expected to achieve LDL-C levels <40 mg/dL (1.0 mmol/L), long-term data from FOURIER will be needed to establish the safety and ASCVD risk-reduction efficacy of dramatically low LDL-C. It is reassuring, however, that individuals homozygous with 2 loss-of-function mutations in PCSK9 appear to be developmentally normal with no evident adverse effects.[40]

All subjects who complete LAPLACE-2 will be invited to participate in a long-term extension study, Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER-2).[41] In addition to LAPLACE-2 and FOURIER,[42] phase 3 trials are underway to examine the efficacy and safety of evolocumab (as a monotherapy, in patients with heterozygous familial hypercholesterolemia and in patients with statin intolerance)[43–45]; these studies will provide additional safety data on dramatically low LDL-C. A phase 3 study examining the effect of evolocumab on plaque regression (measured by intravascular ultrasound) is also underway and will provide data on how PCSK9 inhibition alters the burden of coronary atherosclerosis.[46]


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